REMARKS

This is a response to the Final Rejection dated March 13, 2007, (hereinafter the "Final Rejection"). Claims 1-5, 7, 9-20 and 38-41 are currently pending in the present application.

Rejections under 35 U.S.C. § 103(a)

Claims 1-5, 9-20, and 38-41 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Patent No. 6,162,801, issued to Kita (hereinafter "Kita"), U.S. Patent no. 5,141,741 (hereinafter "Ishida"), U.S. Patent no. 5,650,137 (hereinafter "Nguyen"), U.S. Patent no. 6,051,602 (hereinafter "Bissett"), the abstract of "Radioprotection by Antioxidants," Weiss et al., *Ann. N Y Acad. Sci.*, vol. 899, pp. 44-60 (2000) (hereinafter "Weiss"), U.S. Patent No. 5,776,460, issued to Kim et al. (hereinafter "Kim"), Darr, D. et al., *British Journal of Dermatology* 1992, *127*, 247-253 (hereinafter "Darr"), Shimoi, K., et al., *Mutation Research* 1996, *350*, 153-161 (hereinafter "Shimoi") and "A Fact Sheet on the Health Effects from Ionizing Radiation" (EPA 402-F-98-010) (hereinafter "EPA Fact Sheet"). This rejection is respectfully traversed and reconsideration is requested for the reasons which follow.

According to MPEP §2143:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.
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> The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The rejection does not set forth a case of *prima facie* obviousness since the references, taken in combination with the knowledge generally available to one of ordinary skill in the art, fail to:

(1) teach or suggest all of the limitations of the claims,

(2) constitute analogous art;

(3) provide a suitable motivation to combine the compositions of the cited references; and

(4) provide any expectation of success for combining the cited references.

The Examiner relies on a combination of Kita, Ishida, Nguyen and Bissett to formulate the rejection of the subject matter of claim 1 (see pages 3-4 of the Final Rejection). The present claims require a method for the treatment of radiation injury wherein the radiation injury results from one or more types of radiation selected from the group consisting of proton radiation, fluoroscopic radiation, alpha radiation, beta radiation and gamma radiation. All of Kita, Ishida, and Nguyen relate to compositions used for UV-A and UV-B ultraviolet radiation. Accordingly, none of the references relied on in support of the rejection of claim 1 teaches or suggests a method for the treatment of an injury resulting from one or more of proton radiation, fluoroscopic radiation, alpha radiation, beta radiation and gamma radiation. Therefore, this feature of claim 1 is completely absent from the cited references. For this reason alone, the Examiner has not made out a case of *prima facie* obviousness.

The Examiner attempts to overcome this deficiency in the rejection by taking the position that,

> "...each of the aforementioned components have been taught to be used for radioprotection. Vitamin D3 is known to be useful for the protection and treatment of harmful UV radiation. Antioxidants such as vitamin C (ascorbic acid) are known to be useful in the treatment and the protection of UV radiation-induced damage." (page 6 of the Final Rejection, emphasis added).

It is clear that the cited prior art relates to treatment of UV radiation-induced damage. Thus, the Examiner's generalization of the teachings of this prior art to "radioprotection" is not correct since the prior art cited against claim 1 does not teach treatment of injury due to any form of radiation other than UV radiation-induced damage. In addition, a skilled person would not conclude that treatments for UV radiation-induced damage would be useful for treatment of damage due to other types of radiation, in contrast to the position taken by the Examiner.

More specifically, the attached declaration of Dr. William McBride (hereinafter "the McBride Declaration") indicates that this assumption made by the Examiner is incorrect. Specifically, Dr. McBride states that:

> The type of damage caused by one or more of proton radiation, fluoroscopic radiation, alpha radiation, beta radiation and gamma radiation (ionizing radiation) is significantly different from the type of damage caused by UV-A ultraviolet radiation, UV-B ultraviolet radiation or infrared radiation (non-ionizing radiation). This is most obvious in the case of individuals who are genetically susceptible to non-ionizing radiation. They are not particularly susceptible to ionizing radiation and vice-versa. As a result, a skilled person aware that a

> particular treatment that might protect against injuries due to any of UV-A ultraviolet radiation, UV-B ultraviolet radiation or infrared radiation would not draw the conclusion that the same treatment would be effective for an injury caused by one or more of proton radiation, fluoroscopic radiation, alpha radiation, beta radiation and gamma radiation. (Paragraph 4 of the McBride Declaration)

This evidence demonstrates that a skilled person would not conclude that treatments for UV radiation-induced damage would be useful for an injury caused by one or more of proton radiation, fluoroscopic radiation, alpha radiation, beta radiation and gamma radiation, since the type of injury caused by these significantly different forms of radiation is different.

Kita discloses a topical or external (See col. 1, lines 6-7 of Kita) dermatological composition for protecting the skin against harmful ultraviolet light (See col. 4, lines 14-16 of Kita). The composition of Kita treats ultraviolet induced skin damage resulting from rays within the neighborhood of 260 nm (See col. 8, lines 49-54 of Kita) by using vitamin D, vitamin K and their analogues as a means for absorbing ultraviolet radiation (See col. 4, lines 40-44; col. 8, lines 49-54 Kita). In relation to these teachings of Kita, the attached declaration of Dr. William McBride (hereinafter "the McBride Declaration") states:

> Based on the disclosure of Kita a skilled person would not employ vitamin D_3 compounds for preventing injury due to any of proton radiation, fluoroscopic radiation, alpha radiation, beta radiation and gamma radiation. This is because Kita teaches that vitamin D_3 compounds should be topically applied to provide protection against UV radiation because vitamin D_3 compounds absorb radiation having wavelengths of 240-290 nm. (See col. 1, lines 25-29, col. 6, lines 17-29 and col. 8, lines 49-62 of Kita). Skilled persons are aware that proton radiation, fluoroscopic radiation, alpha radiation, beta radiation and gamma radiation do not have wavelengths in the range of 240-290 nm. Skilled persons would learn from Kita that vitamin D_3 compounds would not absorb any of proton radiation, fluoroscopic radiation, alpha radiation, beta radiation and gamma radiation. Thus, skilled persons familiar with Kita would not consider vitamin D_3 compounds useful to provide protection against any of proton radiation, fluoroscopic radiation, alpha radiation, beta radiation and gamma radiation. (Paragraph 7 of the McBride Declaration)

This evidence clearly shows that the Examiner's reliance on Kita for use of vitamin D_3 to treat an injury due to any of proton radiation, fluoroscopic radiation, alpha radiation, beta radiation and gamma radiation is clearly in contradiction with the common general knowledge of the skilled person.

The Examiner also notes that Kita, in summarizing the prior art, mentions that therapeutic vitamin D may be administered orally or by injection (See col. 1, lines 42-44 of Kita). The oral administration of therapeutic vitamin D mentioned in Kita is said to be useful for treating rickets, osteomalacia, osteoporosis, osteatis, fibrosa, osteosclerosis, bone diseases, malignant tumors (See col. 1, lines 15-24 of Kita). In regard to this teaching, Dr. McBride states that:

> A skilled person would not be motivated to orally administer vitamin D compounds such as vitamin D_3 for the purpose of preventing or treating radiation injury due to proton radiation, fluoroscopic radiation, alpha radiation, beta radiation and gamma radiation based on this teaching of Kita since the injuries caused by these types of radiation are not among the indications listed in Kita for oral therapeutic administration of vitamin D.

Accordingly, the Examiner's reliance on this teaching of Kita is also incorrect since no relationship has been shown between the types of injuries treated by oral administration of therapeutic vitamin D as disclosed in Kita, and the types of injuries claimed in the present claim 1.

Ishida discloses a topical (See col. 6, lines 22-24 of Ishida) anti-sunburn composition for protecting the skin from ultraviolet light (See col. 1, lines 5-15 of Ishida) which includes a conventional ultraviolet absorber and ultraviolet scattering agent (See col. 6, lines 11, 12 of Ishida). The composition of Ishida is directed to treating skin damage caused by UV-A light (See col. 1, lines 67-68 of Ishida). Specifically, Ishida describes an anti-sunburn skin care preparation which contains, as the ultraviolet-absorbing and shielding ingredient, a salt of ellagic acid with a polyvalent metal. Ishida indicates that the polyvalent metal salt of ellagic acid is compounded in a skin care preparation (See col. 4, lines 57-60 of Ishida). Ishida also indicates that,

> Various ingredients in conventional skin-care preparations have [sic – having] no particular reactivity with the ellagic acid compound and can be used without limitations including…vitamins…Usable vitamins include vitamin A, vitamin B, vitamin C, vitamin D, vitamin E, vitamin F, vitamin K, vitamin P, vitamin U, … α-lipoic acid … and derivatives thereof and the like.

(See col. 4, lines 62-65, col. 5, lines 2-3 and col. 5, line 65 to col. 6, line 1 of Ishida). Thus, Ishida teaches that α-lipoic acid and various vitamins can be used to make a conventional skin care preparation in which the active ingredient of the Ishida composition, namely, the polyvalent salt of ellagic acid, may be compounded.

In view of these teachings of Ishida, Dr. McBride states that:

> A skilled person reading Ishida et al. would conclude that α-lipoic acid and the listed vitamins are known to be useful in conventional skin care preparations. A skilled person would thus have no reason whatsoever to include these materials in an oral composition as in the present application since oral compositions are not skin care compositions and are not topically applied to the skin as are skin care compositions. (Paragraph 12 of the McBride Declaration)

In addition, Dr. McBride also notes that,

> A skilled person reading Ishida et al. also would have no reason to expect that α-lipoic acid or the listed vitamins would be useful for the prevention or treatment of any injury caused by proton radiation, fluoroscopic radiation, alpha radiation, beta radiation and gamma radiation since Ishida et al. does [not] provide any information that would indicate to a skilled person that these materials would be useful for this purpose and because skilled persons are not aware of any connection between skin care preparations and oral treatments for injury due to ionizing radiation. (Paragraph 13 of the McBride Declaration)

Accordingly, Ishida does not contain any teachings that would lead a skilled person to employ α-lipoic acid in the method of the present invention.

Nguyen discloses a primarily topical (See col. 4, lines 66-67; col. 5, lines 1-7 of Nguyen) cosmetic composition for protecting the skin from the effects of free radicals induced by atmospheric pollutants or ultraviolet radiation (See col. 1, lines 9-29 of Nguyen). In the examples, the composition of Nguyen is used to treat skin damage caused by UV-A exposure (See col. 8, line 19 of Nguyen). Nguyen appears to state that French patent application no. 2,693,904 discloses the use of chlorophyllins for restructuring skin and preventing aging of the skin (See col. 2, lines 12-14 of Nguyen). Nguyen also mentions that porphyrins can be combined with superoxide dismutase to synergistically reinforce the anti-free radical action of the superoxide dismutase (See col. 2, lines 4-9 and 20-27 of Nguyen).

In regard to the teachings of Nguyen, Dr. McBride states that,

> A skilled person reading Nguyen et al. would not conclude that chlorophyllin, used alone, would have protective effects against UV radiation. This is because Nguyen et al. do not indicate that chlorophyllin, used alone, has any effect in relation to UV radiation. In addition, a skilled person reading Nguyen et al. would have no indication that chlorophyllin could be used to prevent or treat injury caused by proton radiation, fluoroscopic radiation, alpha radiation, beta radiation and gamma radiation since Nguyen et al. does not mention any of these types of radiation nor does Nguyen et al. contain any indication that chlorophyllin

> would be useful to treat an injury that would be caused by these types of radiation. (Paragraph 15 of the McBride Declaration).

Accordingly, Nguyen does not contain any teachings which would be considered by a skilled person to be relevant to the presently claimed invention.

Thus, from the foregoing discussion, it is clear that Kita, Ishida and Nguyen are non-analogous art since the claimed types of radiation and the types of injury that result therefrom are different from the types of radiation and types of injury that are addressed by Kita, Ishida and Nguyen. In addition, from the evidence presented above, it is clear that there is no motivation to combine Kita, Ishida and Nguyen for the purpose of providing a method for the treatment of radiation injury due to one or more of proton radiation, fluoroscopic radiation, alpha radiation, beta radiation and gamma radiation. Finally, from the evidence presented above, it is also clear that a skilled person would have no expectation of successfully treating an injury caused by one or more of proton radiation, fluoroscopic radiation, alpha radiation, beta radiation and gamma radiation, in view of the teachings of Kita, Ishida and Nguyen.

Finally, the Examiner also takes the position that,

> "US Environmental Protection Agency discloses that ionizing radiation of primary concern are alpha, beta, gamma and x-rays, which can original from natural sources or can be technologically produced. Therefore, one of ordinary skill in the art would have had a reasonable expectation to provide or improve the therapeutic effect in preventing injury as a result of proton, fluoroscopic, alpha, beta and gamma radiation..." (Final Rejection, page 7)

The Examiner apparently relies on EPA for the proposition that since ionizing radiation may be technologically produced or may originate from natural sources, the non-ionizing ultraviolet radiation injury patients contemplated in Kita, Ishida, Nguyen, Bissett, Kim and Darr would also be in need of treatment for ionizing radiation injury, thereby creating an overlapping patient population. First, this proposition is merely an unsupported conjecture. Moreover, the argument is irrelevant since neither the EPA nor the other cited references expressly or implicitly teach using the composition of claim 1 for specifically treating an injury resulting from proton radiation, fluoroscopic radiation, alpha radiation, beta radiation or gamma radiation.

This is confirmed by the McBride Declaration where Dr. McBride states that,

> The fact that a human employing one or more of the topical compositions of the cited prior art for protection from ultraviolet radiation may potentially be exposed to some ionizing radiation in the course of their daily routine and is not injured,

> would not be sufficient evidence for a skilled person to draw the conclusion that the topical compositions were also effective to treat or prevent injuries due to ionizing radiation. Although some ionizing radiation is present in the environment, the environmental levels of such radiation are too low to cause any obvious radiation injury. Thus, unless it can be verified that a particular person was exposed to a significant dose of ionizing radiation from the environment, there is insufficient evidence for a skilled person to conclude that a particular topical composition employed for ultraviolet radiation protection would be effective for treatment of an injury due to one or more of proton radiation, fluoroscopic radiation, alpha radiation, beta radiation and gamma radiation. Indeed, because of the known physical differences between ionizing and non-ionizing types of radiation discussed above, a skilled person would not conclude that topical treatment agents employed for ultraviolet protection would be effective against ionizing radiation. (Paragraph 19 of the McBride Declaration)

Thus, this argument made by the Examiner is not based in fact since the levels of ionizing radiation in the environment are too low for skilled persons to draw conclusions about the effectiveness of UV radiation treatments for ionizing radiation.

Accordingly, favorable consideration and withdrawal of the rejection under 35 U.S.C. 103 of independent claim 1 of the present application is requested for these reasons. All of the remaining rejected claims depend on claim 1 and thus are also considered to be patentable for at least these reasons.

With respect to claim 7, Bissett discloses a topical (See col. 3, lines 14-15 of Bissett) composition for regulating various skin conditions such as aging caused by environmental damage and extrinsic factors such as ultraviolet radiation from sun exposure (See col. 1, lines 28-31; col. 3, lines 49-55 of Bissett) which typically produces wavelengths within the UV-A and UV-B range. Bissett also states that,

> It has now been found that topical compositions containing select flavonoid compounds provide benefits in regulating skin condition [sic]... for example, such compositions regulated the signs of skin aging, especially visible and/or tactile discontinuities in skin texture associated with aged skin, including fine lines and wrinkles. (See col. 1, lines 54-60 of Bissett).

In view of these teachings of Bissett, Dr. McBride indicates that,

> Skin aging is not an injury caused by one or more of proton radiation, fluoroscopic radiation, alpha radiation, beta radiation and gamma radiation (ionizing radiation) and thus the skilled person would have no reason to employ flavonoids to treat or reduce injuries due to ionizing radiation.

> Important to note is that Bissett specifically mentions two types of radiation that cause skin aging, namely, ultraviolet radiation and infrared radiation (see col. 1, lines 27-32 of Bissett), but does not mention any of the types of radiation that are claimed in the present patent application. This confirms that Bissett does not consider flavonoids useful for treatment of injuries due to one or more of proton radiation, fluoroscopic radiation, alpha radiation, beta radiation and gamma radiation since Bissett elected not to mention any of these types of radiation among the several types of radiation that were expressly mentioned in Bissett as causing skin aging. (Paragraphs 17-18 of the McBride Declaration).

Accordingly, Bissett teaches away from using flavonoids for treatment of injuries due to one or more of proton radiation, fluoroscopic radiation, alpha radiation, beta radiation and gamma radiation. For this additional reason, the rejection of claims 7 and 9 should be withdrawn.

Kim discloses a processed ginseng product (See col. 3, lines 8-11). Kim also broadly acknowledges that ginseng is known in the art to have a variety of pharmacological effects such as protection of radiation injury (See col. 1, liens 23-27).

Darr discloses topically applying (See page 250) a vitamin C composition to reduce ultraviolet radiation induced skin damage (See page 247) resulting from exposure to UV-B (See pg. 247).

Kim and Darr fail to disclose a method for treating ionizing radiation injuries, specifically injuries resulting from proton radiation, fluoroscopic radiation, alpha radiation, beta radiation or gamma radiation.

Although Weiss, Shimoi and EPA discuss ionizing radiation, they fail to provide a motivation to modify the non-ionizing ultraviolet radiation injury treatments of Kita, Ishida, Nguyen, Bissett, Kim and Darr to arrive at the present invention, particularly in view of the fact that the types of injuries caused by the two distinct types of radiation are different (See paragraph 4 of the McBride Declaration).

Weiss, which fails to disclose the composition of claim 1, teaches that antioxidant nutrients may reduce cellular damage induced by ionizing radiation and/or may have some functionality as a radioprotector. Shimoi, which fails to disclose the composition of claim 1, teaches gastric intubation of tea infusions and plant flavonoids prior to gamma radiation, suggesting that plant flavonoids may have some radioprotective effects. Contrary to the Office Action, it would not be obvious to combine the compositions of the cited references merely because they are "useful for the same purpose", that of treating radiation injury. As discussed

above, while Kita, Ishida, Nguyen, Bissett, Kim and Darr are directed to a treatment for non-ionizing ultraviolet radiation injury, Weiss and Shimoi are directed to a distinctly different application for treating ionizing radiation injury. The differences between these types of injury are confirmed by the McBride Declaration. Therefore, these two sets of references are not directed to the same medical application nor are they useful for the same purpose. The references, therefore, fail to provide sufficient motivation to combine the composition of Kita, Ishida, Nguyen, Bissett, Kim and Darr with Weiss' and Shimoi's ionizing radiation injury treatment.

Additionally, because Kita, Ishida, Bissett, Weiss, Shimoi and EPA fail to disclose an oral composition, there is no reasonable expectation of success for combining the components of the cited references to formulate an oral composition. As discussed above, Kita, Ishida and Bissett are directed to a topical composition. Nugyen also primarily contemplates a topical composition, and Shimoi discloses administration by gastric intubation, whereas Weiss fails to disclose any means of administration.

It is well established and known in the art, contrary to the Examiner's assertion otherwise, that a topical formulation of a compound, which has been found effective in preventing or treating a disease, is not predictive of the effectiveness of the same compound for preventing or treating the same disease when administered orally. Darr even supports a finding that the pharmacological efficacy of a composition is affected by the route of administration and that it would be non-obvious to reformulate a topical ultraviolet blocking composition for oral administration. Specifically, Darr states that, "We believed that topical application would achieve a much higher tissue concentration of this vitamin compared with oral intake. Experiments are in progress to specifically test this." (See page 251 of Darr).

The FDA also supports this position by requiring an additional administrative protocol for drug applications which claim different routes of administration (See 21 C.F.R. §314.54; FDA Unapproved Drug Decision Tree), Thus, the FDA prohibits approval of an abbreviated new drug application, which modifies only the dosage form/route of a previously approved drug, without further efficacy testing (See 21 C.F.R. §314.54; FDA Unapproved Drug Decision Tree).

Moreover, Kita and Ishida teach topical compositions and compounds for absorbing ultraviolet radiation. The ultraviolet radiation is effectively blocked from infiltrating the body by virtue of the fact that the topical compounds provide a physical barrier between the body and

source of radiation. The present claims relate to an oral administration of the composition, wherein the chemical components are not located between the source of radiation and the body. Therefore it would be non-obvious to a person skilled in the art to combine the topical compounds of the cited references for use as an oral formulation.

II. Conclusion

For the reasons set forth above, the method of independent claim 1 and the claims that depend therefrom are inventive over the cited prior art references. Favorable consideration and issuance of a Notice of Allowance is requested.

Respectfully submitted,

Dated: October 31, 2007

Kevin J. Dunleavy
Reg. No. 32,024

KNOBLE YOSHIDA & DUNLEAVY, LLC
Customer No. 21,302
Eight Penn Center, Suite 1350
1628 John F. Kennedy, Jr. Blvd.
Philadelphia, PA 19103
Phone: (215) 599-0600
Fax: (215) 599-0601

Enclosures:

1. Declaration of Dr. William McBride,
2. 21 C.F.R. §314.54, and
3. FDA Unapproved Drug Decision Tree.